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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/619,426	07/16/2003	Kevin J. Tracey	9511-104-27 CONT	7322

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EXAMINER	
GRAFFEO, MICHEL	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 12/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/619,426	TRACEY ET AL.	
	Examiner	Art Unit	
	Michel Graffeo	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/20/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Action

The preliminary Amendment (Filed 29 April 2004) canceled claims 1-9. Claims 10-19 are pending and examined.

Disclosure

The disclosure is objected to under 37 CFR 1.71, as being so incomprehensible as to preclude a reasonable search of the prior art by the examiner. For example, the following items are not understood: formula 1 and formula 2.

Applicant is required to submit an amendment which clarifies the disclosure so that the examiner may make a proper comparison of the invention with the prior art.

Applicant should be careful not to introduce any new matter into the disclosure (i.e., matter which is not supported by the disclosure as originally filed).

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. [1] as follows: Applicant's claim to priority of 60/031061 via US Patent No. 6,143,728 and US Patent No. 6,673,777 must be included on the first page of the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating HIV, does not reasonably provide enablement for the treatment of all diseases characterized by activation along the MAP signal cascade nor a treatment which targets up or downstream activation along the p38 pathway. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2nd 1400 (Fed. Cir. 1988) as to undue experimentation.

The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the art in the assessment of undue experimentation.

1) the nature of the invention; the invention is directed to the treatment of a disease characterized by activation along the MAP signal cascade and a treatment which targets up or downstream activation along the p38 pathway.

2) the breadth of the claims; the scope of the method claims includes the treatment of all a disease characterized by activation along the MAP signal cascades and all treatments which target up or downstream activation along the p38 pathway.

3) the predictability or unpredictability of the art; the ability of treating all diseases characterized by activation along the MAP signal cascades is not yet known in the art. The burden of enabling one skilled in the art to treat all diseases characterized by activation along the MAP signal cascades and all treatments which target up or downstream activation along the p38 pathway would be much greater than that of enabling the treatment of certain diseases wherein the mechanism of action, dosage regime and patient population are known. In other words, although the claim is directed to treating a disease based on the disease characteristics, there is no teaching in the specification for the treatment of other diseases involving the MAP signaling cascade nor the avoidance, for example, of contraindicative reactions using the guanylhydrazone compounds for treating inflammation, cancer or the like (see Levine et al.

Mitoguazone therapy in patients with refractory or relapsed AIDS-related lymphoma: results from a multicenter phase II trial.J Clin Oncol. 1997 Mar;15(3):1094-103. which discloses the side effects of the guanylhydrazone mitoguazone which will exclude patient populations which are sensitive thereto).

In the instant case, the specification does not provide guidance as to how one skilled in the art would accomplish the objective of treating all diseases characterized by activation along the MAP signal cascade. Nor is there any guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active ingredients for treating all disease characterized by activation along the MAP signal cascade and all treatments which target up or downstream activation along the p38 pathway.

Specifically, it is highly unlikely, and the Office would require experimental evidence to support the contention that the claim specified actives could actually treat all diseases characterized by activation along the MAP signal cascade by simply administering, by any method, an amount of the claim specified active agents. The specification fails to enable one of ordinary skill in the art to practice the presently claimed method for treating all disease characterized by activation along the MAP signal cascade.

4) the amount of direction or guidance presented; the specification does not provide any guidance in terms of treating all diseases characterized by activation along the MAP signal cascade. In particular, the specification provides enablement for the treatment of HIV alone.

5) the presence or absence of working examples; no working examples are provided for treating all diseases characterized by activation along the MAP signal cascade, for example in a patient, in the specification. The applicant has not provided any competent evidence or disclosed any tests that are highly predictive for the treatment of such a variety of diseases of the instant claims. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

6) the quantity of experimentation necessary; the quantity of experimentation would be an undue burden to one of ordinary skill in the art and amount to the trial and error type of experimentation. Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention and unpredictability of treating all aforementioned diseases, and the lack of working examples regarding the activity as claimed, one skilled in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

In consideration of each of factors 1-6, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

To satisfy the written description requirement, applicant must convey with reasonable clarity to one skilled in the art, as of the filing date that application was in possession of the claimed invention. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

Possession may be shown in many ways. For example, possession may be shown by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would

recognize that the inventor had possession of the claimed invention. For example, a specification may describe an actual reduction to practice by showing that the inventor constructed an embodiment or performed a process that met all the limitations of the claim and determined that the invention would work for its intended purpose or an applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole.

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is

substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]."

Applicant has not conveyed possession of the invention with reasonable clarity to one skilled in the art. The targeting activation of an upstream or downstream component along the p38 cascade does not indicate with any clarity the mechanism of the invention or where or how the targeting is occurring.

Claims 10 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "characterized" is unclear in because the claim can be interpreted as requiring that the disease is caused by activation along a signal transduction cascade or in the alternative as having the same downstream effects, for example, as a disease caused by activation along a signal transduction cascade.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bianchi et al. An inhibitor of macrophage arginine transport and nitric oxide production (CNI-1493) prevents acute inflammation and endotoxin lethality. Molecular Medicine (Baltimore, MD, United States) (1995), 1(3), 254-66 in view of US Patent No. 6,218,136 to Kumar et al. further in view of Kumar et al. Activation of the HIV-1 Long Terminal Repeat by Cytokines and Environmental Stress Requires an Active CSBP/p38 MAP Kinase. The Journal of Biological Chemistry (271), No 48. pp 30864-30869. 29 Nov 1996.

Bianchi et al. teach that CNI-1493 prevents NO production which participates in the regulation of the synthesis of TNF and other cytokines (in current claims 10-19; see page 263 – CNI-1493 in Endotoxic Shock).

Bianchi et al. do not teach the method of treating HIV for example.

The '136 Patent teaches that p38 is activated in response to TNF (in current claims 10-19; see Abstract).

Kumar et al. teach that inhibitors of p38 inhibit the replication of HIV in response to TNF (in current claims 10-19; see page 30868).

Although none of the references teach a combination therapy, it is prima facie obvious to combine CNI-1493 with an anti-viral agent specifically HIV therapies since combining agents which are known to be useful as HIV treatments individually into a singe composition useful for the very same purpose is prima facie obvious. See In re Kerkhoven 205 USPQ 1069. Since it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining a p38 inhibitor with an HIV therapy flows logically from their having been individually taught in the prior art.

As combined the references teach that CNI-1493 modulates TNF and that the modulation of TNF results in treating HIV.

One of ordinary skill in the art would have been motivated to combine the above references and as combined would teach the invention as claimed. One of ordinary skill in the art would have been motivated to combine the references because the '136 Patent and Kumar et al. are both directed to inhibitors of p38 and TNFs involvement relative thereto. Kumar et al. additionally teach that the p38 inhibitor SB203580 inhibits TNF. Bianchi et al. provides an additional compound which modulates TNF. Thus, the

combined references teach and make prima facie obvious how to use the claimed invention at the time that it was made.

US Patent No. 5,854,289 to Bianchi et al. is considered an equivalent to Bianchi et al. An inhibitor of macrophage arginine transport and nitric oxide production (CNI-1493) prevents acute inflammation and endotoxin lethality. Molecular Medicine (Baltimore, MD, United States) (1995), 1(3), 254-66.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michel Graffeo whose telephone number is 571-272-8505. The examiner can normally be reached on 9am to 5:30pm Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

MG

Christopher S. F. Low

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

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1 December 2005
MG